Adjustment of DXA BMD Measurements for Anthropometric Factors and its Impact on the Diagnosis of Osteoporosis

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Mini Abstract

We compared the effect of anthropometric factors on osteoporosis diagnosis by QCT and DXA and found QCT spine vBMD was not associated with body weight, BMI or DXA anteroposterior spine thickness. In contrast, DXA spine and hip aBMD were strongly associated with all three factors. Adjustment of DXA aBMD measurements improved consistency with QCT vBMD.

Abstract

Purpose Although the diagnosis of osteoporosis using DXA T-scores preferentially targets patients with lower body mass index (BMI), there is evidence that obesity is not protective against fractures. The aim of this study was to compare the effect of anthropometric factors on osteoporosis diagnosis by QCT and DXA and investigate whether adjustment of DXA aBMD can achieve a more even distribution of diagnoses between slimmer and heavier individuals consistent with QCT.

Methods The participants were 964 men and 682 women referred for low dose chest CT and DXA examinations as part of their employers' health check-up programs. QCT vBMD was measured in the L1-L2 vertebrae and DXA aBMD in the spine and hip. The prevalence of osteoporosis in each tertile of BMI in participants aged >50 years was evaluated based on their QCT and DXA findings, and then re-evaluated after adjustment to the mean BMI in each sex. Similar investigations were performed for body weight and DXA anteroposterior (AP) spine thickness. The effect of the adjustment of DXA aBMD for anthropometric factors on the correlation with QCT vBMD was also examined.

Results For spine QCT correlations of age adjusted vBMD residuals against BMI were not statistically significant in men (P=0.44) or women (P=0.32). In contrast, slopes for aBMD residuals were all highly statistically significant (P<0.001). There were similar findings for weight and AP spine thickness. Adjustment of DXA aBMD for anthropometric factors resulted in a more equal spread of diagnoses of osteoporosis and greater consistency with QCT.

Conclusion Our study highlights differences between DXA and QCT in their correlation with anthropometric factors and its effect on the diagnosis of osteoporosis. Adjustment of DXA T-scores for anthropometric factors gave greater consistency with QCT vBMD. Further

studies are required into whether adjusting DXA aBMD for anthropometric factors has a beneficial impact on the discriminative or predictive power for vertebral fracture.

Key Words: DXA; QCT; Body weight; BMI; Spine thickness; Diagnosis; Osteoporosis

Introduction

With the ageing of society, osteoporosis has become a significant health problem around the world [1-3]. Bone mineral density (BMD) plays a central role in the diagnosis of osteoporosis, the estimation of fracture risk and the monitoring of treatment [1,2,4,5]. BMD is the mass of bone mineral per unit volume [the volumetric density (vBMD) in units of mg cm^{-3}] measured by quantitative computed tomography (QCT), or per unit area [the areal density (aBMD) in units of g cm^{-2}] measured by dual energy X-ray absorptiometry (DXA). Although both can be measured in vivo by densitometric techniques, DXA is the most widely used method around the world and is recommended by all osteoporosis guidelines [1,2,6]. Although QCT has the advantage of measuring the true volumetric BMD and separating trabecular bone from cortical bone [7], it features less prominently in guidelines [2,5,8,9]. However, in daily clinical practice CT examinations of the abdomen and thoracic region are more frequently performed than DXA and present a valuable and underutilised opportunity to acquire measurements of hip and spine vBMD [10,11].

Although DXA scans predict fracture risk [12], due to their two-dimensional projection nature, DXA derived aBMD measurements are subject to a number of limitations [4]. Areal aBMD measures the superposition of cortical and trabecular bone and results are dependent on bone size. Carter et al. proposed the use of bone mineral apparent density (BMAD, g cm^{-3}) to compensate for differences in bone size by correcting aBMD for the anteroposterior (AP) spine thickness [13]. Absorptiometric measurements at the spine and hip are also influenced by variations in soft tissue thickness and composition because DXA

manufacturers' algorithms make assumptions about the homogenous disposition of fat in the body that in reality are not true [4]. Studies of the accuracy errors in DXA aBMD measurements at the spine and hip caused by soft tissue inhomogeneity suggest that these can be substantial [14-16]. Recent studies suggest that obesity may be a risk factor for vertebral fracture [17-19]. Liu et al. proposed the use of weight corrected bone mineral content (wBMC) to reduce the over-diagnosis of osteoporosis in lighter weight patients and its under-diagnosis in heavier patients [20]. Even with the known dependence of aBMD data on bone size and body weight, all the national and international osteoporosis guidelines continue to recommend the use of DXA aBMD measurements without any adjustment for BMI, weight or bone size [1,2,6].

The adjustment of vBMD and aBMD measurements for anthropometric factors such as BMI, weight and AP spine thickness and their impact on the diagnosis of osteoporosis has not been investigated before using QCT and DXA scans in the same population. Therefore, in the present study we sought to determine the effect of BMI, weight and bone size on vBMD by QCT and aBMD by DXA using data from a healthy Chinese population referred for their annual health check-up. After finding that all three factors were significant predictors of DXA aBMD, but not for QCT vBMD, we explored the impact of the adjustment of DXA aBMD for anthropometric factors on the diagnosis of osteoporosis and the correlation between aBMD and QCT vBMD.

Material and Methods

Participants

The study was approved by the ethics committee of Beijing Jishuitan Hospital and each participant gave written informed consent for their data to be used. Participants were a subset of the China Biobank project, a prospective nationwide multi-centre cohort study

registered with the US clinical trials database (clinicaltrials.gov; trial identifier: NCT03699228) [21]. The subjects were >30 years old and were originally referred to the health management centres of the affiliated hospital of Guiyang Medical University, and the affiliated Yijishan Hospital of Wannan Medical University, as part of their employers' health check-up programs, and received a low dose chest CT (LDCT) scan for lung cancer screening and a DXA examination for the measurement of aBMD with both scans performed on the same day. Subjects with metal implants within the CT or DXA scan fields were excluded. A total of 964 men and 682 women were included in the study, which involved the post-scan processing of CT and DXA scans. No additional radiation was involved.

Anthropometry measurements

Weight (kg) and height (m) were measured using calibrated digital scales and stadiometers and body mass index was calculated [BMI = weight (kg)/height $(m)^2$]. Following the definition of BMAD by Carter et al., DXA AP spine thickness was defined as the square root of the average projected area of the L2-4 vertebra [√(L2-4 area/3)] [13].

QCT and DXA scans

The details of the China Biobank study protocol have been published elsewhere [21]. All participants in this study received an annual health check-up as part of their employer's workplace welfare scheme. LDCT scans were conducted on a Supria CT scanner (Hitachi, Tokyo, Japan) at the Guiyang centre and an Optima CT540 CT scanner (GE Healthcare, WI, USA) at the Wannan centre. LDCT is now the standard for lung cancer screening [22] and the subsequent analysis of these CT scans enabled evaluation of vBMD at L1 and L2 using the Mindways QCT Pro software calibrated with a QCT phantom (Mindways, Austin, TX, USA) [21]. The regions of interest were defined as the oval-shaped areas containing the largest area

of trabecular bone in the mid-plane of each vertebral body, not including cortical bone or the basivertebral plexus.

DXA measurements of aBMD and lumbar spine projected area were conducted using GE Lunar DXA (GE Lunar Prodigy and DPX Bravo DXA scanners, GE Healthcare, WI, USA) systems, GE Lunar Encore software and GE Lunar positioning devices to enable consistency and accuracy of patient positioning. The lumbar spine (L2-4) scan was performed at the Wannan Centre, and scans of the lumbar spine (also L2-4) and hip were performed at the Guiyang Centre. DXA and LDCT were performed on the same day. All data were transferred to the Data Management Centre (Beijing Jishuitan Hospital) for data cleaning and analysis.

Statistical Analysis

All statistical analyses were performed using Microsoft Excel and the Vassarstats statistical computation web browser [23]. Where descriptive data were normally distributed results were described as the mean and standard deviation (SD) and analysed using parametric statistical tests. Otherwise, data were described by the median and analysed using non-parametric tests.

BMD measurements at each site were plotted against age and fitted by linear regression. In men, QCT spine vBMD values declined linearly with age between 30 and 60 years, with a slower rate of loss in those aged >60 years, and the data were fitted in two segments. For DXA spine aBMD, a number of the men age >70 years had elevated BMD results attributed to degenerative disease. Therefore men in this age group were excluded from further analysis and the data for men <70 years fitted by a single regression line. DXA femoral neck and total hip BMD were both fitted by a single regression line over all ages. For women the plots of QCT vBMD and DXA aBMD against age were fitted in three segments: a constant BMD for

women aged <45 years, a linear decrease from age 45 to 60, and a shallower linear decrease in those aged >60. Since QCT and DXA measurements have different units (mg cm^{-3} and g cm^{-2} respectively) the residuals from the linear regression lines were converted into Z-scores by dividing by the young adult population SD (QCT: 25 mg cm^{-3}, spine DXA and femoral neck DXA in women: 0.12 g cm^{-2}, other DXA sites: 0.13 g cm^{-2}). Z-scores for each sex and skeletal site were plotted against age to confirm that the mean Z-score and slope of the regression line were both zero.

Z-scores were also plotted against weight, height, BMI and AP spine thickness. At each DXA site the correlation coefficient was largest for the scatter plot against weight, least for the plot against height and intermediate for BMI and spine thickness (Table 1). Weight, BMI and spine thickness were therefore selected as anthropometric factors for further analysis and the slopes of their regression lines with Z-score and their standard errors (SE) evaluated for men and women for QCT and each DXA site. From this analysis it was unclear whether a linear relationship between Z-score and the anthropometric measurement applied over the entire range. For weight this relationship was examined by dividing subjects into 10 kg intervals (men: 40-49, 50-59, 60-69, 70-79, 80-89 and 90+ kg; women 40-49, 50-59, 60-69, 70-79 and 80+ kg) and the mean Z-score and SE for each bin plotted against weight. Chi-squared tests were performed to evaluate the goodness of fit of the points to a straight line.

The prevalence of osteoporosis in men and women aged 50 years and over was evaluated based on their QCT and DXA findings. For QCT, osteoporosis was defined as vBMD <80 mg cm^{-3}. For DXA, T-scores were calculated using the GE-Lunar China reference ranges and osteoporosis defined according to the WHO Task Group criterion of a spine or femoral neck T-score < -2.5 [4]. For each anthropometric factor (weight, BMI or spine thickness) participants were divided into three equal tertiles and the prevalence of osteoporosis diagnosed by QCT or DXA evaluated for each tertile. For DXA measurements

the prevalence of osteoporosis was re-evaluated after spine and femoral neck BMD values were adjusted for weight, BMI or spine thickness to their average value in men and women respectively. Results for the different tertiles were compared in a 3 x 2 contingency table using Fisher's exact test. To further evaluate the effects of adjusting DXA aBMD values, QCT vBMD measurements of participants were plotted against DXA spine T-scores, femoral neck T-scores and the lower of the two T-scores. The correlation coefficients for each sex were evaluated before and after adjustment for weight, BMI and spine thickness and the statistical significance of the difference between the two correlation coefficients determined [24]. A P-value < 0.05 was taken to be statistically significant.

Results

A total of 964 men and 682 women received QCT and DXA lumbar spine bone density measurements. Of these, 635 men and 402 women also received DXA hip measurements. Table 2 gives the participants' descriptive statistics.

Figure 1A shows the scatter plot of DXA spine Z-score against age for men. Points plotted in red for the men >70 years old included a number of individuals with high Z-scores suggestive of spinal degenerative disease, and these individuals were removed from further analysis. For the men <70 years the mean Z-score and the slope of the regression line of Z-score against age were both zero. Plots of Z-score against age for women and for QCT and hip DXA in men did not show any similar anomaly.

Figure 1B shows the scatter plot for DXA spine Z-score against body weight for the men <70 years old in Figure 1A together with the linear regression line (solid red line) and 95% confidence interval (dashed red lines). The slope and standard error were 0.0393 ± 0.0038 Z-score units per kg. Similar results with slopes 8 to 10 times greater than the standard error where found for the other DXA measurements. However, slopes of Z-score against

weight for spine QCT in men (P = 0.82) and women (P = 0.30) were not significantly different from zero. Findings for plots of QCT and DXA Z-scores against BMI and spine thickness were similar to those for weight (Figures 1C,D).

Figures 2A-C compare the slopes of the QCT and DXA Z-score regression lines in men and women at the different measurement sites for the three anthropometric factors together with their 95% confidence intervals (CI). In Table 3 the same slopes are listed in BMD units (for example g/cm^2 per kg instead of Z-score units per kg) together with the values of the population SD used to convert Z-scores into BMD units.

Figure 3 shows the mean Z-score in each 10 kg interval of body weight plotted against mean weight for the QCT spine and DXA spine and femoral neck sites in men and women respectively. The error bars show the 95% CI. In each plot the red line is the linear regression line evaluated as shown in Figure 1B. For each BMD site the results of the chi-squared test show that the regression line is a good fit to the data points. Results for the total hip site (not shown) were similar to the femoral neck.

The percentages of men and women aged 50 years and over with osteoporosis in each tertile of body weight, BMI and AP spine thickness are plotted in Figures 4A-C respectively. Each panel of Figure 4 compares the prevalence of osteoporosis in each tertile for QCT vBMD (left-hand set of three points), conventional DXA aBMD (middle set of three points), and DXA aBMD adjusted for the respective anthropometric factor (right-hand set of three points). Error bars show the 95% CI. DXA aBMD measurements were adjusted to the mean value of the anthropometric factor in each sex. Further details including the adjustment factors are given in the caption to Figure 4. The overall prevalence of osteoporosis diagnosed by QCT was 16.3% in women and 5.4% in men, and for DXA was 15.6% in women and 3.0% in men. When women were broken down into tertiles of body weight the prevalence of

osteoporosis as diagnosed by QCT was independent of weight (P = 0.89), while for conventional DXA there was a statistically significant trend for the prevalence of osteoporosis to decrease at higher weights (P = 0.026) that was no longer significant after adjusting aBMD values for weight (P = 0.31). The number of men with osteoporosis was too low for any of the differences to be statistically significant. The findings for tertiles of BMI and spine thickness were similar (Figure 4B,C). When the highest and lowest tertiles were compared using 2 x 2 contingency tables the P-values of the unadjusted vs. adjusted DXA results were 0.013 vs. 0.29, 0.0019 vs. 0.29 and 0.019 vs. 1.0 for weight, BMI and spine thickness respectively.

When the correlation coefficients of DXA spine T-score, femoral neck T-score and the lower of the two T-scores against QCT spine vBMD were plotted for men and women before and after adjustment for anthropometric factors there was a trend for the correlation coefficients to increase after adjustment and half the increases were statistically significant (P < 0.001) (Figure 5).

Discussion

This study aimed to investigate the influence of anthropometric factors such as body weight, BMI and AP spine thickness on the diagnosis of osteoporosis by QCT and DXA in a large cohort of healthy Chinese subjects. The overall prevalence of osteoporosis was similar in both sexes whether it was diagnosed by QCT or DXA. However, when participants were divided into tertiles of weight, BMI or spine thickness the prevalence of osteoporosis diagnosed by QCT was consistent across all three tertiles, while for DXA there were pronounced gradients with subjects with lower weight, BMI or spine thickness having a higher prevalence of osteoporosis compared with those with larger values. When DXA measurements were adjusted for weight, BMI or spine thickness using slopes of regression lines like those shown in Figure 1 the prevalence of osteoporosis was reduced in the lower

tertile and increased in the higher tertile and findings were more consistent with those for QCT. There was also a trend for adjusted DXA T-scores to correlate more strongly with QCT vBMD, and in half the correlations the increases were statistically significant.

DXA uses attenuation measurements at two X-ray photon energies to minimise the influence of different soft tissue thickness and body composition over the scan area on the accuracy of aBMD measurements [25]. DXA aBMD measurements are the product of the average volumetric BMD and AP bone thickness in each pixel averaged over the bone region of interest (ROI). As such, measurements are sensitive to bone size as well as the true volumetric BMD making it more complicated to interpret results in children compared with adults and explaining some of the differences in reference ranges between men and women and between different ethnic groups. In contrast, QCT measures the true volumetric BMD independently of bone size or the thickness and composition of extraosseous soft tissue. The dependence of DXA aBMD on AP bone thickness and inhomogeneity in body composition may explain the striking differences compared with QCT in the correlation coefficients in Table 1 and slopes in Figure 2. The slopes of the regression lines with body weight in Figure 2A are similar for the spine and hip sites and between men and women. This suggests that a variation of bone size with body weight may be a factor in explaining the weight correlations found for DXA. Another explanation might be the increased stresses put on bone in heavier individuals, although it is notable that the absence of any effect on QCT measurements excludes an effect of body weight on spinal trabecular vBMD. A third explanation might be that in heavier individuals there is a systematic difference in the thickness of adipose tissue (AT) between the bone and soft tissue reference ROIs [14-16] and the effect of increasing BMI on aBMD is a soft tissue measurement error rather than a real difference. Tothill et al. estimated that 10 mm of AT thickness was equivalent to -0.043 g/cm^2 of hydroxyapatite[14], meaning that the slope of the aBMD regression lines with body weight in Table 2 could be

explained by AT thickness differences of 11 to 15 mm per 10 kg increase in body weight. Further investigations of this issue could include direct measurements of bone sizes using CT images, a comparison of integral aBMD in the hip measured with QCT compared with DXA, or measurements of adipose tissue thickness and its variation with BMI using CT or MRI imaging.

Carter et al. were the first to compensate for differences in bone size by dividing aBMD by the square root of the projected area to give an estimate of volumetric BMD referred to as bone mineral apparent density (BMAD) [13]. Unlike QCT and DXA BMD measurements, there is no accepted threshold for the diagnosis of osteoporosis using BMAD. For this reason we used the DXA AP spine thickness defined as the square root of the average projected area of the L2-4 vertebrae as an anthropometric factor predicted to correlate with DXA spine aBMD. Mean value of L2-4 BMAD for the study participants was 0.28 g cm^{-3} in men and 0.29 g cm^{-3} in women, comparable to the spine aBMD adjustment factor of 0.23 g cm^{-3} inferred from the scatter plots (Table 3). Unsurprisingly, the bone thickness inferred from spine DXA measurements did not correlate as well with aBMD measurements made in the hip (Table 1 and Table 3).

Recently, Liu et al. proposed the use of weight corrected bone mineral content (wBMC) in the spine and hip obtained by dividing the BMC in each ROI by body weight [wBMC = BMC/weight (g/kg)] so that body weight rather than projected area is used for BMC standardisation [20]. They showed that defining osteoporosis in terms of wBMC T-scores removed the trend with conventional DXA aBMD for a greater proportion of patients in the lower tertile of body weight to be diagnosed with osteoporosis than those in the upper tertile, resulting in a more even distribution of diagnoses across the full range of body weights similar to that for QCT in Figure 4 of the present paper. Our use of the slopes of the regression lines of anthropometric factors to adjust DXA aBMD measurements had a similar

effect in re-balancing the prevalence of osteoporosis, ensuring a more equal spread of diagnoses and greater consistency with QCT.

The findings of Liu et al. [20] and the difference between QCT and DXA in the distribution of cases of osteoporosis across the range of body weights raises the question of whether there is any justification for the goal of levelling out diagnoses of osteoporosis across different body weights, or whether the present bias with DXA that directs anti-fracture therapies preferentially towards lower weight patients achieves the best overall clinical outcome. Since the aim of fracture prevention is paramount, this is an issue that can only be decided using fracture data. There is evidence that, despite greater soft tissue mass and thickness, obesity is not protective against fracture, particularly at the spine and appendicular skeletal sites [17-19]. A recent study in Shanghai, China, reported that the prevalence of vertebral deformity in men was similar to that in women (17% vs. 17.3%) over 60 years [26] and a three-fold higher vertebral fracture prevalence in men has been reported elsewhere [17]. The application of a body weight or BMI correction for DXA BMD measurements may improve the identification of people at risk of fracture, especially in obesity, which has been identified as a risk factor for falls in men [27]. The fact that QCT vBMD is not associated with body weight indicates that heavier weight does not have a beneficial effect on spine trabecular vBMD, suggesting it may not be protective against fracture. Our findings suggest that the ability of weight, BMI or spine thickness corrected aBMD to predict fracture risk warrants further investigation.

Our findings may have further relevance. The WHO diagnostic criteria for osteoporosis and osteopenia were developed and validated on data for postmenopausal women and then extended to men without the same rigorous validation seen in women. One consequence is that the prevalence of osteoporosis in men may be higher than that currently projected by WHO T-scores at around one-fifth the rate in women [3]. The mean weight of men in our

study was 13 kg heavier than women, and adjustment of men's results to the mean body weight in women may re-dress this imbalance. Our findings may have relevance for the longitudinal monitoring of aBMD, particularly in populations where large changes in body weight are expected, such as in patients undergoing bariatric surgery, in cancer patients after chemotherapy and in children [28-32]. The rapid decline in the BMD of these patients may reflect more the influence of weight loss on the aBMD measurement than their true bone loss, especially given that QCT assessment of vBMD has demonstrated a negligible decline compared with aBMD [29-32].

Our study has several limitations. Firstly, this is a cross sectional study and no fracture information was available. Therefore, it was not possible to compare the performances of raw DXA aBMD, adjusted aBMD and QCT vBMD for predicting fracture risk. Further studies are required into whether obesity is a protective factor against fractures and whether adjusting DXA aBMD for anthropometric factors has a beneficial impact on the discriminative or predictive power for vertebral fracture. Secondly, there were few men with osteoporosis. It was necessary to exclude men over 70 years old from the DXA spine analysis because of the high incidence of spinal osteoarthritis in these participants and their consequent elevated BMD findings. Failure to exclude these men would have prejudiced the power of the study to explore the relationship between body weight and spine aBMD.

In conclusion, in this study we report that, after adjustment for gender and age, QCT spine vBMD was not associated with body weight, BMI or spine bone thickness. In contrast, after adjustment for gender and age, DXA spine and hip aBMD were strongly associated with all three anthropometric factors. We determined adjustment factors for body weight of 0.005 g cm^{-2} kg^{-1} and 0.006 g cm^{-2} kg^{-1} for men and women respectively, for BMI of 0.013 g cm^{-2} kg^{-1} m^2 in both sexes, and for spine thickness of 0.23 cm^{-1} for spine aBMD and 0.15 cm^{-1} for hip BMD. The application of these coefficients to adjust DXA aBMD measurements can help

rebalance the diagnosis and management of osteoporosis between patients with higher and lower than average body size making DXA outcomes more consistent with QCT vBMD. Further studies are required into whether adjusting DXA aBMD for anthropometric factors has a beneficial impact on the discriminative or predictive power for vertebral fracture.

Conflicts of interest: Ling Wang, Limei Ran, Xiaojuan Zha, Kaiping Zhao, Yingying Yang, Qing Shuang, Yandong Liu, Karen Hind, Xiaoguang Cheng and Glen M Blake declare that they have no conflicts of interest.

References

1. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8:136. doi:10.1007/s11657-013-0136-1

2. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N, National Osteoporosis Guideline G (2017) UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 12 (1):43. doi:10.1007/s11657-017-0324-5

3. Zeng Q, Li N, Wang Q, Feng J, Sun D, Zhang Q, Huang J, Wen Q, Hu R, Wang L, Ma Y, Fu X, Dong S, Cheng X (2019) The Prevalence of Osteoporosis in China, a Nationwide, Multicenter DXA Survey. J Bone Miner Res 34 (10):1789-1797. doi:10.1002/jbmr.3757

4. Kanis JA, Gluer CC (2000) An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of Scientific Advisors, International Osteoporosis Foundation. Osteoporos Int 11 (3):192-202. doi:10.1007/s001980050281

5. Engelke K, Lang T, Khosla S, Qin L, Zysset P, Leslie WD, Shepherd JA, Schousboe JT (2015) Clinical Use of Quantitative Computed Tomography (QCT) of the Hip in the Management of Osteoporosis in Adults: the 2015 ISCD Official Positions-Part I. J Clin

Densitom 18 (3):338-358. doi:10.1016/j.jocd.2015.06.012

6. Research CSoOaBM (2017) Primary osteoporosis treatment guide. Chin J Osteoporos Bone Miner Res 5 (10). doi:10.3969/j.issn.1674-2591.2017.05.002

7. Link TM (2012) Osteoporosis imaging: state of the art and advanced imaging. Radiology 263 (1):3-17. doi:10.1148/radiol.12110462

8. Engelke K, Adams JE, Armbrecht G, Augat P, Bogado CE, Bouxsein ML, Felsenberg D, Ito M, Prevrhal S, Hans DB, Lewiecki EM (2008) Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. J Clin Densitom 11 (1):123-162. doi:10.1016/j.jocd.2007.12.010

9. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/qct.pdf?la=en.

10. Jang S, Graffy PM, Ziemlewicz TJ, Lee SJ, Summers RM, Pickhardt PJ (2019) Opportunistic Osteoporosis Screening at Routine Abdominal and Thoracic CT: Normative L1 Trabecular Attenuation Values in More than 20 000 Adults. Radiology 291 (2):360-367. doi:10.1148/radiol.2019181648

11. Smith AD (2019) Screening of Bone Density at CT: An Overlooked Opportunity. Radiology 291 (2):368-369. doi:10.1148/radiol.2019190434

12. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ, 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Predictive value of BMD for hip and other fractures. J Bone Miner Res 20 (7):1185-1194. doi:10.1359/JBMR.050304

13. Carter DR, Bouxsein ML, Marcus R (1992) New approaches for interpreting projected bone densitometry data. J Bone Miner Res 7 (2):137-145. doi:10.1002/jbmr.5650070204

14. Tothill P, Pye DW (1992) Errors due to non-uniform distribution of fat in dual X-ray absorptiometry of the lumbar spine. Br J Radiol 65 (777):807-813. doi:10.1259/0007-1285-65-777-807

15. Svendsen OL, Hassager C, Skodt V, Christiansen C (1995) Impact of soft tissue on in vivo accuracy of bone mineral measurements in the spine, hip, and forearm: a human

cadaver study. J Bone Miner Res 10 (6):868-873. doi:10.1002/jbmr.5650100607

16. Tothill P, Weir N, Loveland J (2014) Errors in dual-energy X-ray scanning of the hip because of nonuniform fat distribution. J Clin Densitom 17 (1):91-96. doi:10.1016/j.jocd.2013.02.008

17. Rudman HA, Birrell F, Pearce MS, Tuck SP, Francis RM, Treadgold L, Hind K (2019) Obesity, bone density relative to body weight and prevalent vertebral fracture at age 62 years: the Newcastle thousand families study. Osteoporos Int 30 (4):829-836. doi:10.1007/s00198-018-04817-3

18. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, Pfeilschifter J, Silverman S, Diez-Perez A, Lindsay R, Saag KG, Netelenbos JC, Gehlbach S, Hooven FH, Flahive J, Adachi JD, Rossini M, Lacroix AZ, Roux C, Sambrook PN, Siris ES, Glow I (2011) Obesity is not protective against fracture in postmenopausal women: GLOW. Am J Med 124 (11):1043-1050. doi:10.1016/j.amjmed.2011.06.013

19. Hind K, Pearce M, Birrell F (2017) Total and Visceral Adiposity Are Associated With Prevalent Vertebral Fracture in Women but Not Men at Age 62 Years: The Newcastle Thousand Families Study. J Bone Miner Res 32 (5):1109-1115. doi:10.1002/jbmr.3085

20. Liu TT, Li XD, Wang WZ, Zhang JG, Yang DZ (2019) Efficacy of weight adjusted bone mineral content in osteoporosis diagnosis in Chinese female population. Chin Med J (Engl) 132 (7):772-781. doi:10.1097/CM9.0000000000000143

21. Wu Y, Guo Z, Fu X, Wu J, Gao J, Zeng Q, Fu H, Cheng X (2019) The study protocol for the China Health Big Data (China Biobank) project. Quant Imaging Med Surg 9 (6):1095-1102. doi:10.21037/qims.2019.06.16

22. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, Lammers JJ, Weenink C, Yousaf-Khan U, Horeweg N, van 't Westeinde S, Prokop M, Mali WP, Mohamed Hoesein FAA, van Ooijen PMA, Aerts J, den Bakker MA, Thunnissen E, Verschakelen J, Vliegenthart R, Walter JE, Ten Haaf K, Groen HJM, Oudkerk M (2020) Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 382 (6):503-513. doi:10.1056/NEJMoa1911793

23. http://www.vassarstats.net.

24. Blake GM, Fogelman I (1997) Technical principles of dual energy x-ray absorptiometry. Semin Nucl Med 27 (3):210-228. doi:10.1016/s0001-2998(97)80025-6

25. Lee IA, Preacher KJ (2013) Calculation for the test of the difference between two dependent correlations with one variable in common [computer software]. Available from http://quantpsy.org

26. Gao C, Xu Y, Li L, Gu WQ, Yi CT, Zhu Q, Gu HA, Chen BH, Wang QQ, Tang F, Xu JL, Hou JM, Song HJ, Wang H, Wang ZL, Zhang ZL (2019) Prevalence of osteoporotic vertebral fracture among community-dwelling elderly in Shanghai. Chin Med J (Engl) 132 (14):1749-1751. doi:10.1097/CM9.0000000000000332

27. Hooker ER, Shrestha S, Lee CG, Cawthon PM, Abrahamson M, Ensrud K, Stefanick ML, Dam TT, Marshall LM, Orwoll ES, Nielson CM, Osteoporotic Fractures in Men S (2017) Obesity and Falls in a Prospective Study of Older Men: The Osteoporotic Fractures in Men Study. J Aging Health 29 (7):1235-1250. doi:10.1177/0898264316660412

28. Liu C, Wu D, Zhang JF, Xu D, Xu WF, Chen Y, Liu BY, Li P, Li L (2016) Changes in Bone Metabolism in Morbidly Obese Patients After Bariatric Surgery: A Meta-Analysis. Obes Surg 26 (1):91-97. doi:10.1007/s11695-015-1724-5

29. Ivaska KK, Huovinen V, Soinio M, Hannukainen JC, Saunavaara V, Salminen P, Helmio M, Parkkola R, Nuutila P, Kiviranta R (2017) Changes in bone metabolism after bariatric surgery by gastric bypass or sleeve gastrectomy. Bone 95:47-54. doi:10.1016/j.bone.2016.11.001

30. Gagnon C, Schafer AL (2018) Bone Health After Bariatric Surgery. JBMR Plus 2 (3):121-133. doi:10.1002/jbm4.10048

31. Lindeman KG, Greenblatt LB, Rourke C, Bouxsein ML, Finkelstein JS, Yu EW (2018) Longitudinal 5-Year Evaluation of Bone Density and Microarchitecture After Roux-en-Y Gastric Bypass Surgery. J Clin Endocrinol Metab 103 (11):4104-4112. doi:10.1210/jc.2018-01496

32. Saad R, Habli D, El Sabbagh R, Chakhtoura M (2019) Bone Health Following Bariatric Surgery: An Update. J Clin Densitom. doi:10.1016/j.jocd.2019.08.002

Tables

Table 1: Pearson correlation coefficients of body weight, body mass index (BMI), DXA spine (L2-4) thickness and height with QCT and DXA BMD Z-score

		Pearson Correlation Coefficient with Z-score†			
Gender	BMD site	Weight	BMI	DXA Spine Thickness‡	Height
Men	DXA Spine	0.322 (P<0.001)	0.259 (P<0.001)	0.261 (P<0.001)	0.168 (P<0.001)
	DXA Fem Neck	0.362 (P<0.001)	0.275 (P<0.001)	0.191 (P<0.001)	0.220 (P<0.001)
	DXA Total Hip	0.388 (P<0.001)	0.347 (P<0.001)	0.147 (P<0.001)	0.151 (P<0.001)
	QCT Spine	0.007 (P=0.82)	0.025 (P=0.44)	-0.068 (P=0.035)	-0.023 (P=0.47)
Women	DXA Spine	0.305 (P<0.001)	0.217 (P<0.001)	0.266 (P<0.001)	0.171 (P<0.001)
	DXA Fem Neck	0.399 (P<0.001)	0.347 (P<0.001)	0.213 (P<0.001)	0.119 (P=0.017)
	DXA Total Hip	0.406 (P<0.001)	0.398 (P<0.001)	0.241 (P<0.001)	0.037 (P =0.50)
	QCT Spine	0.040 (P=0.30)	0.038 (P=0.32)	0.068 (P=0.078)	0.009 (P=0.82)

†: Z-scores calculated after adjusting BMD for age and normalizing to the population standard deviation values listed in Table 3

‡: DXA spine thickness defined as √(L2-4 projected area/3)

Table 2: Descriptive statistics of subjects (mean and SD)

	Men	Women	P-value
N	964	682	
Age (y)	50.8 (10.2)	52.6 (10.5)	P < 0.001
Weight (kg)	70.3 (9.6)	57.3 (8.1)	P < 0.001
Height (m)	1.68 (0.06)	1.56 (0.06)	P < 0.001
BMI (kg m^{-2})	24.8 (3.0)	23.6 (3.2)	P < 0.001
DXA Spine Area (L2-4) (cm^2)	46.3 (3.9)	39.4 (3.6)	P < 0.001
DXA Spine Thickness (cm)	3.93 (0.16)	3.56 (0.16)	P < 0.001
QCT vBMD L1-2 mg cm^{-3}	130.4 (31.4)	126.2 (43.6)	P = 0.022
DXA aBMD L2-4 g cm^{-2}	1.124 (0.152)	1.070 (0.180)	P < 0.001
DXA aBMD femoral neck g cm^{-2}	0.920 (0.134)	0.858 (0.136)	P < 0.001
DXA aBMD total hip g cm^{-2}	0.984 (0.130)	0.912 (0.140)	P < 0.001

BMI: Body mass Index. Among the men 1.5% were underweight (BMI < 18.5), 52.6% were normal (BMI 18.5-24.9), 40.5% were overweight (BMI 25-29.9) and 5.5% were obese (BMI 30-39). For women the percentages were 2.9%, 66.2%, 27.6% and 3.3% respectively.

Table 3: Anthropometric BMD corrections by gender and QCT or DXA BMD measurement site. Slopes for body weight, BMI and spine thickness are expressed in BMD units per kg, per kg m^{-2} and per cm respectively

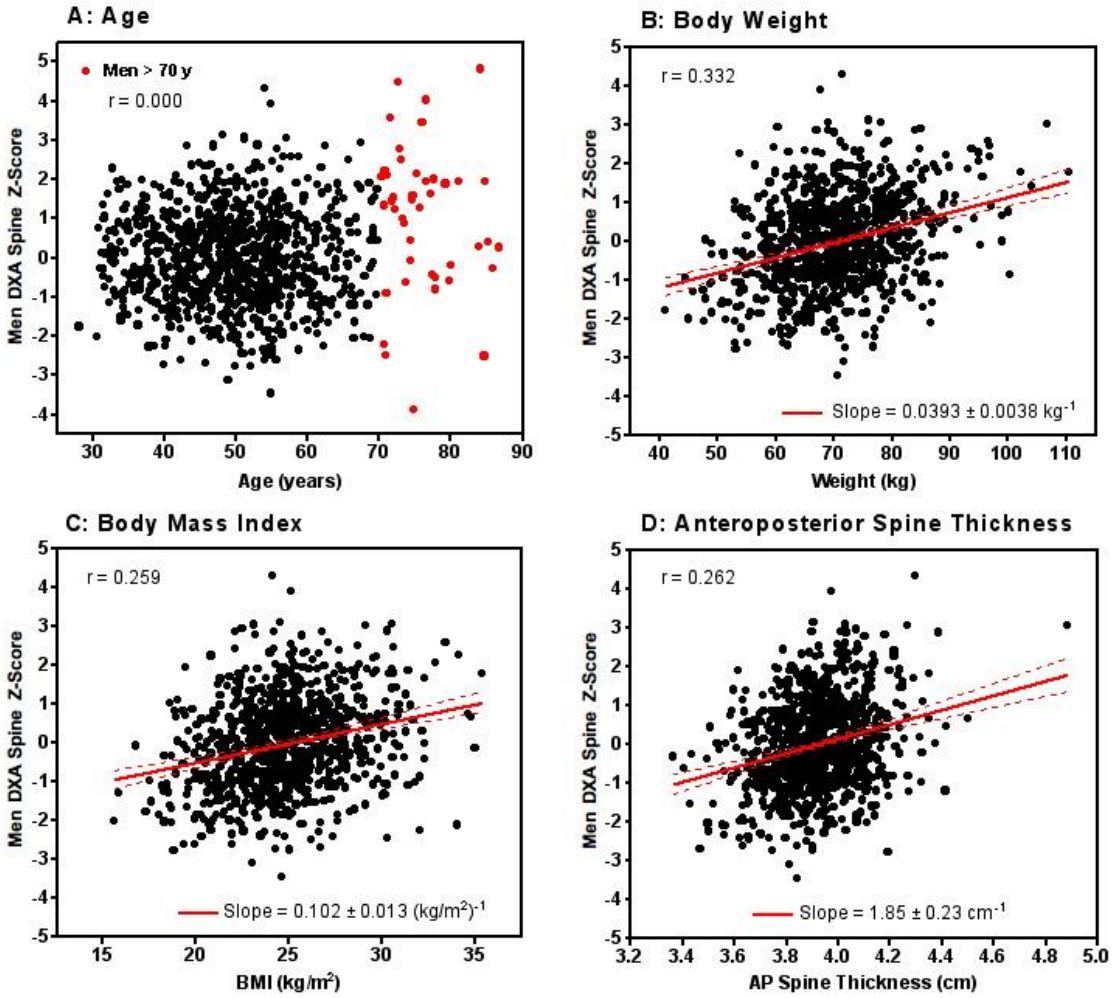
Gender	BMD Site	Population SD ($g\ cm^{-2}$)	Body Weight Slope (SE)* ($g\ cm^{-2}\ kg^{-1}$)	BMI Slope (SE)* ($g\ cm^{-2}\ kg^{-1}\ m^{2}$)	Spine Thickness Slope (SE)* ($g\ cm^{-3}$)
Men	QCT Spine (L1-2)	25†	0.020† (0.087)	0.216† (0.279)	-10.1† (5.1)
	DXA Spine (L2-4)	0.12	0.0047 (0.0005)	0.0122 (0.0015)	0.223 (0.027)
	DXA Femoral Neck	0.13	0.0046 (0.0005)	0.0111 (0.0015)	0.137 (0.028)
	DXA Total Hip	0.13	0.0052 (0.0005)	0.0157 (0.016)	0.111 (0.030)
Women	QCT Spine (L1-2)	25†	0.135† (0.131)	0.327† (0.331)	11.6† (6.5)
	DXA Spine (L2-4)	0.12	0.0056 (0.0007)	0.0101 (0.0017)	0.240 (0.034)
	DXA Femoral Neck	0.12	0.0058 (0.0007)	0.0125 (0.0017)	0.156 (0.039)
	DXA Total Hip	0.13	0.0063 (0.0008)	0.0150 (0.0019)	0.181 (0.040)

* Slopes in BMD units obtained by multiplying the slopes in Z-score units plotted in Figures 1, 2 and 3 by the population SD in column 3.

† BMD units are in mg cm^{-3} rather than g cm^{-2}

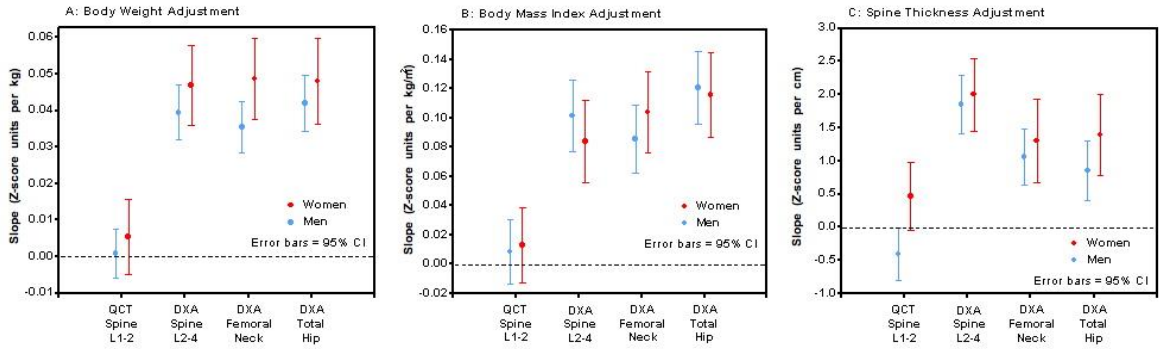
Figure Legends

Figure 1



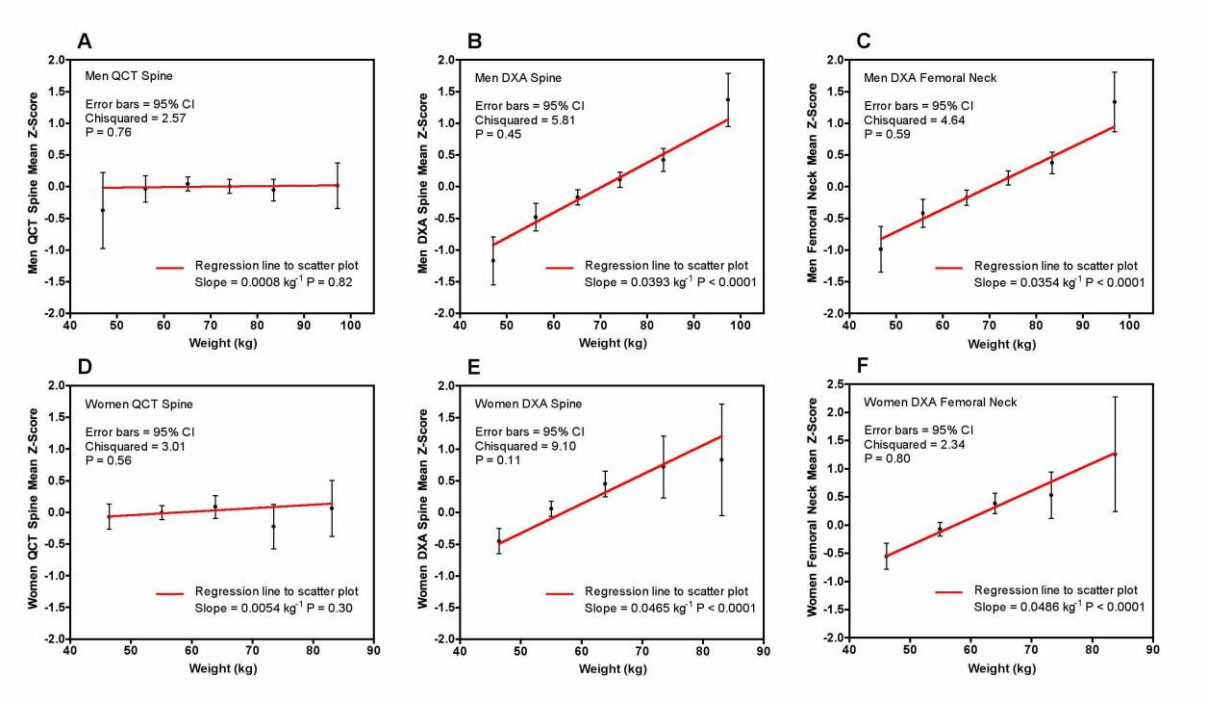
Scatter plots for men of DXA spine aBMD (L2-4) Z-score against: (A) age; (B) body weight; (C) body mass index (BMI); (D) anteroposterior spine thickness expressed as √(L2-4 Area/3). Men over 70 years old plotted as red dots in (A) were excluded from the scatter plots in (B), (C) and (D) because of individuals with high Z-scores likely to be due to degenerative disease. The red continuous lines are the linear regression lines. Red dashed lines show the 95% confidence intervals. The slopes are expressed in Z-score units and the statistical error is ± 1 standard error.

Figure 2



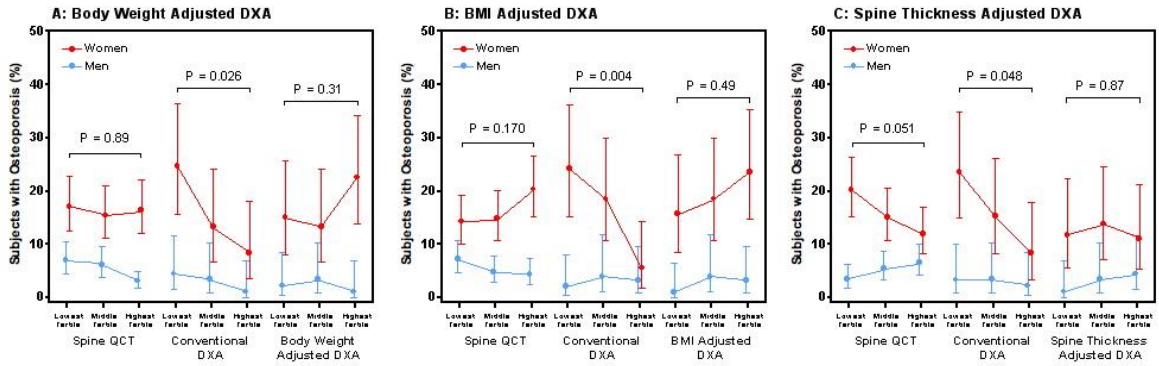
Slopes of Z-score against: (A) body weight; (B) BMI; (C) DXA AP spine thickness for QCT and DXA BMD measurements by gender and measurement site. Values plotted are the results of linear regression analysis similar to that shown for male spine DXA in Figures 1B-D. Error bars are the 95% confidence intervals.

Figure 3



Plots for men and women of mean Z-score in 10 kg intervals of body weight against mean body weight for that interval. Plots are for: (A) QCT spine (L1-2); (B): DXA spine (L2-4); (C) DXA femoral neck in men; (D) QCT spine (L1-2); (E): DXA spine (L2-4); (F) DXA femoral neck in women. Error bars show the 95% confidence intervals. The red lines are the linear regression lines obtained from scatter plots similar to Figure 1B. For each BMD site the results of the chi-squared test show that the regression line is a good fit to the data points

Figure 4



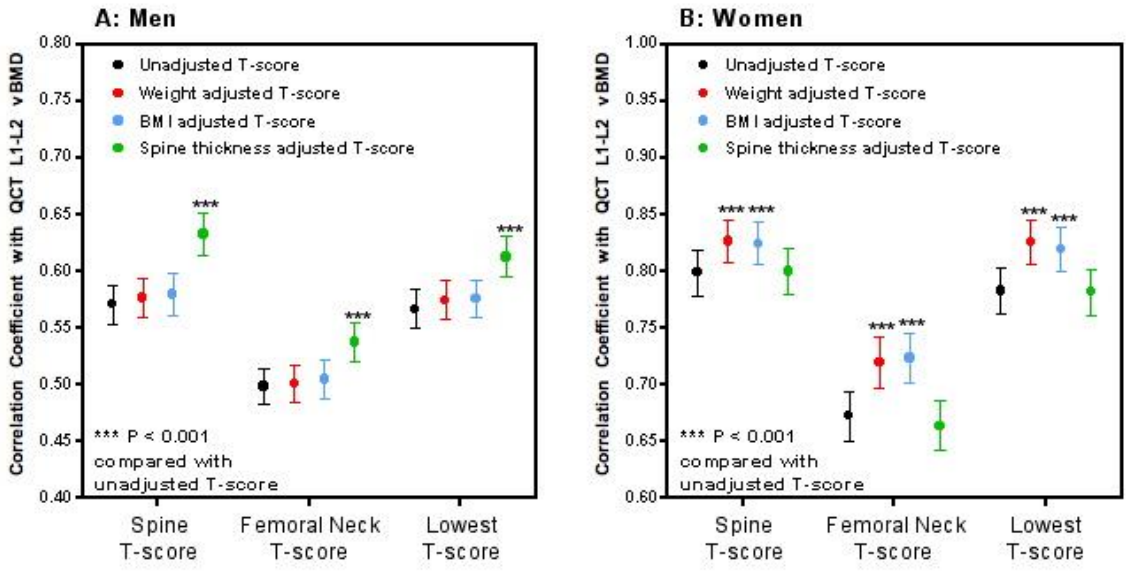
Percentage of women and men aged 50 years and over with osteoporosis plotted for tertiles of (A) body weight; (B) BMI; (C) AP spine thickness [= √(L2-4 Area/3)]. In each panel the left-hand set of three points refer to QCT spine vBMD, the middle three points to conventionally interpreted DXA aBMD, and the right-hand three points to DXA aBMD adjusted for the respective anthropometric factor. Error bars show the 95% confidence intervals. For QCT, osteoporosis was defined as a mean trabecular vBMD in the L1-2 vertebrae < 80 mg cm^{-3}. For DXA, osteoporosis was defined as a T-score at the spine (L2-4) or femoral neck T < -2.5. P-values are the statistical significance of the difference in each set of three tertiles in women evaluated using Fisher's Exact Test. None of the differences in men were statistically significant.

Body weight adjustment: spine and femoral neck DXA aBMD were adjusted to mean weights of 70 kg in men and 58 kg in women using corrections of 0.005 g cm^{-2} kg^{-1} and 0.006 g cm^{-2} kg^{-1} in men and women respectively. For men the lowest, middle and highest tertiles were 41.0-66.0, 66.1-73.9 and 74.0-110.5 kg respectively. In women they were 37.9-53.4, 53.5-59.6 and 59.7-95.5 kg.

BMI adjustment: spine and femoral neck DXA aBMD were adjusted to a mean BMI of 25.0 kg m^{-2} in men and 24.0 kg m^{-2} in women using a correction of 0.013 g cm^{-2} kg^{-1} m^2 in both sexes. For men the lowest, middle and highest tertiles were 15.6-23.9, 24.0-25.9 and 26.0-35.9 kg m^{-2} respectively. In women they were 14.9-22.8, 23.0-25.9 and 26.0-33.8 kg m^{-2}.

Spine thickness adjustment: spine and femoral neck DXA aBMD were adjusted to a mean thickness of 3.9 cm in men and 3.6 cm in women using corrections of 0.23 g cm^{-3} for spine BMD and 0.15 g cm^{-3} for femoral neck BMD in both sexes. For men the lowest, middle and highest tertiles were 3.36-3.88, 3.88-4.01 and 4.01-4.88 cm respectively. In women they were 3.17-3.53, 3.53-3.67 and 3.67-4.04 cm.

Figure 5



Plots of correlation coefficients of DXA spine T-score, femoral neck T-score and the lower of the two T-scores against QCT spine vBMD for: (A) men, and (B) women before and after adjustment for weight, BMI and spine thickness. Error bars show ± 1SE for each correlation coefficient. P-values are the results of comparing adjusted and unadjusted T-scores after testing for the difference between two dependent correlations with one variable in common [25].